No. 6, 2004

News & Issues

This is the final issue of the newsletter for the year 2004. We hope that the information covered has been useful in your work and in keeping abreast of recent developments in drug safety. As stated in the previous issues, we have now established a system for electronic mailing of the newsletter to accommodate those of you who cannot be included in our postal mailing list. To join this list, please send an email to LISTSERV@WHO.INT with the message text: subscribe WHO-PHN.

This has been a busy year with many new priority areas emerging in drug safety. The World Alliance of Patient Safety was launched in October and the WHO drug safety programme will work closely with the Alliance, particularly in reporting medication errors and conducting research on the impact of safety measures in promoting patient safety solutions. The issue of safety of medicines in children, with emphasis on off-label use, is also recognized as an important and neglected area that needs to be brought to the attention of WHO.

The Twenty-seventh Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring was held from 4 to 6 October, in Dublin, Ireland. We include, in this issue, the observations on the questions discussed by the working groups at the meeting. We hope these observations will stimulate innovative and collaborative approaches to pharmacovigilance. Last, but not least, we wish all our readers good health and happiness in 2005.
TABLE OF CONTENTS

REGULATORY MATTERS

ACTRA-RX AND YILISHEN -- Presence of undeclared sildenafil ................................................................. 1
ADALIMUMAB -- Serious infections if used together with anakinra............................................................ 1
ANTIDEPRESSANTS -- Label to warn of increased suicidality in children; Patient Medication Guide to advise on risks and precautions to be taken ............................................................... 1
ATORVASTATIN -- Interaction with grapefruit juice ................................................................................ 2
BLACK COHOSH COMBINATION #2; YELLOW DOCK COMBINATION #3 -- Presence of aristolochic acid........ 2
CELECOXIB -- Withdrawn in Turkey ...................................................................................................... 2
EPOETIN ALFA -- Label change to reflect thrombosis risk ...................................................................... 2
ETANERCEPT, INFlixIMAB -- Reports of serious infections ...................................................................... 2
INFLIXIMAB -- Lymphoma warning added to label ................................................................................... 3
ISOTRETINOIN -- Enhancement to risk management programme ............................................................ 3
LEVOHYROXINE SODIUM -- Dysphagia and risk of choking .................................................................. 3
MIFEPRISTONE -- Important labelling changes proposed ....................................................................... 3
PERGOLIDE MESYLATE -- Label change: risk of cardiac valvulopathy ..................................................... 4
REMINYL AND AMARYL -- Reports of medication errors ........................................................................ 4
VALDECOXIB -- Label updated to warn about skin reactions ................................................................ 4

SAFETY OF MEDICINES

CHOLINESTERASE INHIBITORS -- Reports of cardiac arrhythmias ........................................................... 5
CYCLO-OXYGENASE-2 INHIBITORS -- Plans to review all medicines in this class ........................................ 5
ETHINYLESTRADIOL / CYPROTERONE -- Increased risk of thrombosis ................................................... 5
HERBAL MEDICINES -- Cardiovascular ADRs reported to Health Canada ............................................. 5
INFLUENZA VIRUS VACCINE -- Interactions with drugs ........................................................................ 6
MEDROXYPROGESTERONE -- Effect on bone mineral density ................................................................. 6
PAMIDRONATE DISODIUM, ZOLEDRONIC ACID -- Spontaneous reports of osteonecrosis of the jaw ......... 6
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) -- ADRAC reviews use in children and adolescents . 7
TERBINAFINE -- Reports of blood dyscrasias ......................................................................................... 7
TRICYCLIC ANTIDEPRESSANTS -- Overdose risk ................................................................................... 7

FEATURE

Twenty-seventh Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring: Observations from Working Groups ............................. 8
ACTRA-RX AND YILISHEN

Presence of undeclared sildenafil

USA. The Food and Drug Administration (FDA) has warned consumers not to purchase or to consume Actra-Rx or Yilishen, two products promoted and offered for sale on websites as dietary supplements for treating erectile dysfunction and enhancing sexual performance in men. The FDA has found that these products contain undeclared prescription strength sildenafil. Sildenafil, when taken together with certain prescription drugs containing nitrates (such as nitroglycerin) may cause a significant lowering of blood pressure to an unsafe level. These drugs should therefore be taken only under medical supervision. The FDA is advising consumers who use Actra-Rx or Yilishen to stop taking these products and to consult their health-care providers regarding erectile dysfunction treatment.

Reference:

ADALIMUMAB

Serious infections if used together with anakinra

USA. Abbott Laboratories, in consultation with FDA, has updated the prescribing information for adalimumab with new warnings regarding use with anakinra, hypersensitivity reactions and haematologic events. Adalimumab is indicated for the treatment of rheumatoid arthritis. Serious infections were seen in clinical studies with the concurrent use of anakinra and another Tumor Necrosis Factor (TNF) - blocking agent. Since similar toxicities may occur with the concurrent use of anakinra and other TNF blocking agents, and since adalimumab is also a TNF blocking agent, Abbott Laboratories warn that the combination of anakinra with adalimumab is not recommended. In addition, Abbott is also warning that rare but serious anaphylactic and hypersensitivity reactions as well as haematologic reactions including aplastic anaemia have been reported in patients treated with adalimumab; treatment should be discontinued immediately when such hypersensitivity reactions are observed and patients should be advised to seek medical attention if signs and symptoms of haematologic events (e.g. persistent fever, pallor, bruising, bleeding) are noticed.

Reference:

ANTI-DEPRESSANTS

Label to warn of increased suicidality in children; Patient Medication Guide to advise on risks and precautions to be taken

USA. The FDA has directed manufacturers of all antidepressant drugs to include a boxed warning and expanded warning statements in the labels of these products that alert health-care providers to an increased risk of suicidality in children and adolescents treated with these products and to include additional information about the results of paediatric studies. All drugs included in the general class of antidepressants will have this new boxed and expanded labelling. The risk of suicidality was identified in a combined analysis of short-term placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs), in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD) or other psychiatric disorders. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. According to the FDA Public Health Advisory, the expanded warning statements will highlight the following:

- Antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with MDD and other psychiatric disorders.

- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.

- Patients on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behaviour.

- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

- A statement regarding whether the particular drug is approved for any paediatric indication(s) and, if so, which one(s).

The FDA has advised that a Patient Medication Guide (MedGuide) should be given to all patients receiving the drugs to provide information to patients and their families and caregivers about the risk of suicidality in children and adolescents. MedGuides are intended to be distributed by the pharmacist with each prescription or refill of a medication.
WHO Pharmaceuticals Newsletter No. 6, 2004

REGULATORY MATTERS

**ATORVASTATIN**

Interaction with grapefruit juice

UK. The Summary of Product Characteristics (SPC) for atorvastatin (Lipitor) has been revised to include the interaction between atorvastatin and grapefruit juice. The SPC now states that grapefruit juice contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4.

Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.


**BLACK COHOSH COMBINATION #2; YELLOW DOCK COMBINATION #3**

Presence of aristolochic acid

Canada. The Health Products and Food Branch Inspectorate in Canada has discontinued the manufacturing authorization for Black Cohosh Combination #2 and Yellow Dock Combination #3 products since they have been found to contain asarum. Asarum is known to produce aristolochic acid, a chemical that can cause cancer, mutations in human cells and end-stage kidney failure (see WHO Pharmaceuticals Newsletter No.3, 2002).


**CELECOXIB**

Withdrawn in Turkey

Turkey. The Market Authorization Holder for celecoxib (Celebrex) in Turkey has voluntarily withdrawn celebrex from the Turkish market. The Turkish Human Medicinal Products Advisory Committee had earlier directed that the labels of celecoxib (Celebrex 100 mg and 200 mg) capsules should state that the product may not be used by individuals who have obstructive arterial disorder of the cardiovascular system or the central nervous system.


**EPOETIN ALFA**

Label change to reflect thrombosis risk

Canada. The Canadian product monograph for epoetin alfa (Eprex) has been revised to include information regarding a possible increased incidence of thrombosis in patients with cancer who have high haemoglobin levels (>120 g/L).

The 'Dear Health-care Professional' letter issued by Janssen-Ortho Inc, in consultation with Health Canada, advises that the Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration and Information for the Patient sections have been updated to reflect this safety information.


Reports in WHO-file: Thrombosis 105

**ETANERCEPT, INFLIXIMAB**

Reports of serious infections

Canada. Health Canada has received a total of 1233 reports of suspected adverse drug reactions (ADRs) to etanercept (Enbrel; n = 536) or infliximab (Remicade; 697), from 1 January 2000 to 31 May 2004, 297 of which were infections. For etanercept, 82 of the 109 reports of infection were considered to be serious, and there were seven deaths; for infliximab, 132 of the 188 reports of infection were considered serious, and there were 14 deaths. The various types of infections reported are detailed below (see table).

Reference: Canadian Adverse reaction Newsletter 14, No.4, October 2004.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Etanercept (ADR reports)</th>
<th>Infliximab (ADR reports)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Abscess</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Mycoses</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Pyelonephritis or cystitis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Infectious arthritis</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Encephalitis or meningitis</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Reference: Canadian Adverse reaction Newsletter 14, No.4, October 2004.

**INFLIXIMAB**

Lymphoma warning added to US Remicade label

USA. Centocor, Inc1. has issued a 'Dear Health-care Professional' letter advising that a warning of malignancies has been added to the US infliximab (Remicade) label. Following the evaluation of safety data on tumour necrosis factor (TNF)-antagonists at a US FDA Arthritis Advisory Committee

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1. Centocor, Inc.
REGULATORY MATTERS

ISOTRETINOIN

Enhancement to risk management programme

USA. The Food and Drug Administration (FDA) is strengthening the risk minimization action plan (RiskMAP) for isotretinoin, a drug indicated in the treatment of a severe type of acne that is not responsive to other therapies. The enhanced RiskMAP is expected to reduce the risk of birth defects associated with fetal exposure to isotretinoin and to ensure that patients would receive appropriate counselling and testing to prevent the possibility of birth defects. This programme will include, but will not be limited to the following:

- Registration of all prescribers, patients and dispensing pharmacies in a single centralized clearing house.
- Before a registered pharmacy first dispenses the medication for a particular patient, the following will occur:
  - Completion of patient education by the prescriber;
  - An appropriately timed and documented negative pregnancy test prior to dispensing the medication;
  - Completion of the informed consent, education and risk management components by the patient;
  - Electronic or other verification of the above actions.
- For all subsequent prescriptions, the following will occur monthly:
  - Ongoing patient education by the prescriber;
  - Repeated negative pregnancy test within a specified window prior to dispensing;
  - Completion of the education and risk management components by the patient;
  - Electronic or other verification of the above actions.

The isotretinoin sponsors will play a large role in determining compliance and effectiveness of the strengthened RiskMAP including establishing and maintaining a drug-clearing house, monitoring sales, including sales via the internet and evaluating the effectiveness of the programme in reducing and limiting pregnancy exposures.


LEVOTHYROXINE SODIUM

Dysphagia and risk of choking

USA. Jones Pharma Incorporated has issued a ‘Dear Health-care Professional’ letter advising of changes to the US labelling of levothyroxine sodium (Levoxyl) in response to reports of gagging, choking, ‘tablet stuck in throat’ and dysphagia in patients taking levothyroxine sodium, usually without water. The US package insert has been revised to include a warning that ‘Levoxyl may rapidly swell and disintegrate’ resulting in the above-mentioned adverse events. Patients are strongly advised to take Levoxyl with a full glass of water.


MIFEPRISTONE

Important labelling changes proposed

USA. The FDA has advised important new safety changes to the labelling of mifepristone (Mifeprax, RU-486) approved for the termination of early pregnancy. The existing black box on the product label will be updated with new information on the risk of serious bacterial infections, sepsis, and bleeding and death that may occur following any termination of pregnancy, including use of mifepristone (Mifeprax, RU-486). This revision has been proposed following reports of serious bacterial infections, sepsis, bleeding, ectopic pregnancies that had ruptured, and death. The revised labelling...
will provide physicians and patients with important information so that they can respond and possibly prevent rare but serious complications that may occur with any abortion. The Medication Guide and Patient agreement have also been updated to reflect the new safety information. The FDA will continue to monitor the usage of mifepristone (Mifeprex, RU-486) and may take further action.

Reference:

PERGOLIDE MESYLATE
Label change: risk of cardiac valvulopathy

Canada. Shire BioChem Inc, following discussions with Health Canada, has issued a 'Dear Health-care Professional' letter and a Public Advisory concerning new safety information on pergolide (Permax) and the risk of cardiac valvulopathy. The letter highlights two recent studies that have shown an increased frequency of cardiac valvulopathy associated with pergolide (Permax) compared with non-ergot dopamine agonists. Given the potentially serious nature of these events, the Warnings, Dosage and Administration, Adverse Events, Post-Marketing and Consumer Information sections of the pergolide (Permax) product monograph are to be revised. The new labelling information notes that pergolide (Permax) is not recommended in patients with a history of serious inflammation, fibrosis or cardiac valvulopathy, and physicians are advised to reassess the risks and benefits of pergolide (Permax) compared with non-ergot dopamine agonists. Physicians are also advised to inform patients of the risk of cardiac valvulopathy and other serious fibrotic reactions. Additionally, pretreatment cardiovascular evaluation and periodic monitoring for the development of valvular disease or fibrosis are recommended.

Reference:

REMINYL AND AMARYL
Reports of medication errors

USA. Janssen Pharmaceutica has issued a 'Dear Health-care Professional' letter1 and a 'Dear Pharmacist' letter2 advising of reports of medication errors involving confusion between galantamine (Reminyl) and glimepiride (Amaryl).

These reports include instances where patients received glimepiride (Amaryl), indicated for type 2 diabetes mellitus, in place of galantamine (Reminyl), indicated for mild-to-moderate Alzheimer’s-type dementia, and involved various adverse events (AEs), including severe hypoglycaemia and one case of death1. These errors appear to have arisen from prescriptions that have been written, interpreted, labelled and/or filled incorrectly due to the similarity in the names of these agents.

In the letter to pharmacists, the company offers the following suggestions:

• Place Amaryl and Reminyl apart from each other on the shelf.
• Confirm the brand name prescribed on written and oral prescriptions.
• Counsel patients about the brand name, indication and proper use of each medication2.

References:

VALDECOXIB
Label updated to warn about skin reactions

Worldwide. Pfizer is updating the valdecoxib (Bextra) label worldwide with information on a rare skin reaction, and has advised of an increase in cardiovascular events in patients undergoing coronary bypass surgery who receive either valdecoxib alone or in combination with parecoxib. Data from spontaneous reports show that the skin reaction has been reported at a greater rate with valdecoxib than with other cyclo-oxygenase-2 inhibitors, and that the risk mainly exists in the first two weeks of valdecoxib therapy.

Reference:
SAFETY OF MEDICINES

CHOLINESTERASE INHIBITORS

Reports of cardiac arrhythmias

Australia. The increased cholinergic activity seen with cholinesterase inhibitors may have vagal effects on heart rate (HR), including bradycardia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received a number of reports of cardiac arrhythmias in association with the cholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl), which are increasingly used for Alzheimer’s disease (see table).

<table>
<thead>
<tr>
<th>ADRAC reports of cholinesterase inhibitor-associated arrhythmia</th>
<th>Donepezil</th>
<th>Rivastigmine</th>
<th>Galantamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>14</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AV block</td>
<td>5</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Unspecified arrhythmia</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>MI/cardiac arrest</td>
<td>7</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Reference:

CYCLOOXYGENASE-2 INHIBITORS

Plans to review all medicines in this class

Europe. Following the worldwide withdrawal of rofecoxib (Vioxx), the European Medicines Agency (EMEA) has been asked by the European Commission to conduct a review of all cyclo-oxygenase-2 (COX-2) inhibitor medicines. The Agency’s scientific committee responsible for human medicines (CHMP) will look at newly available data on all aspects of cardiovascular safety of the COX-2 inhibitors celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib, including thrombotic events (heart attack and stroke) and cardiovascular events (e.g. hypertension, oedema and cardiac failure).

The objective of this review is to assess whether there is a need to make changes to existing marketing authorizations including labelling throughout the whole of the European Union and whether additional studies are needed. When completed, the outcome of the review will be posted on the Agency’s website. In the meantime the agency reminds that the earlier warnings, issued on 6 October 2004, remain valid:

- Rofecoxib (Vioxx) has been withdrawn due to serious thrombotic events. Patients on rofecoxib should be reviewed and alternative treatment considered. When considering treatment with other COX-2 inhibitors, prescribers should consult the latest version of the summary of product characteristics, particularly for cardiovascular events.

- Patients who were on rofecoxib should consult their doctor at the next available opportunity to discuss their treatment options.

Reference:

ETHINYLESTRADIOL/CYPROTERONE

Increased risk of thrombosis

Norway. The Norwegian Medicines Control Agency (NMCA) has issued a reminder that ethinylestradiol/cyproterone (Diane) is associated with an increased risk of thrombosis. The NMCA has received 26 reports of adverse reactions associated with Diane, including 15 of venous thrombosis, two of which were fatal. They note that ethinylestradiol/cyproterone (Diane) should be used with the same caution as oral contraceptives, and should not be used in women with known risk factors for thrombosis, such as smoking, obesity and a personal or family history of thrombosis.

Reference:

HERBAL MEDICINES

Cardiovascular ADRs reported to Health Canada

Canada. Health Canada has received 16 cardiovascular ADR reports associated with synephrine- or Citrus aurantium
Medroxyprogesterone Acetate: Effect on Bone Mineral Density

Canada, UK.
Medroxyprogesterone acetate suspension injection (Depo-Provera) may suffer substantial loss in bone mineral density.
• The loss in bone density is greater with increasing duration of treatment.
• The loss in bone density may not be completely reversible.
• It is unknown whether the use of medroxyprogesterone injection (Depo-Provera) during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture in later life.

The product label under the sections of Indications and Clinical Use, Warnings, Dosage and Administration and Adverse Reactions will be appropriately updated to reflect the above findings.

The Chairman of the UK Committee on Safety of Medicines (CSM) has also written to health-care professionals about these recent findings from the clinical studies and the implications therein, while reminding health professionals that the effect of medroxyprogesterone acetate injection (Depo-Provera) on bone mineral density has been recognized for many years. In addition, the CSM also advises that:

- In adolescents, medroxyprogesterone injection (Depo-Provera) may be used as first-line contraception only after other methods have been discussed with the patient and considered to be suitable or unacceptable.
- In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than two years.
- In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.

References:

Pamidronate Disodium, Zoledronic Acid

Spontaneous reports of osteonecrosis of the jaw

USA. In response to spontaneous reports of osteonecrosis of the jaw in patients receiving bisphosphonates, Novartis has issued a ‘Dear Doctor’ letter advising of changes to the US prescribing information for the bisphosphonates pamidronate disodium (Aredia) and zoledronic acid (Zometa). The ‘Precautions’ sections of the US package inserts for both these products now state that there have been reports of osteonecrosis of the jaw involving patients with cancer receiving bisphosphonates, many of whom were receiving concomitant corticosteroids and antineoplastics. Most reports
SAFETY OF MEDICINES

were associated with dental procedures, and the package inserts recommend that patients with risk factors for osteonecrosis undergo dental examination and preventive dentistry prior to starting bisphosphonate therapy, and that invasive dental procedures should be avoided during treatment. It is not known whether discontinuation of bisphosphonates reduces the risk of osteonecrosis in patients requiring dental procedures. Information regarding osteonecrosis has also been included in the 'Post-Marketing Experience' sections of the package inserts.


Reports in WHO-file: Osteonecrosis: Pamidronic acid 54, zoledronic acid 38.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

ADRAC reviews use in children and adolescents

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has issued a statement regarding SSRI use in children and adolescents with major depressive disorder (MDD) and other psychological disorders, following a review of data in paediatric patients. ADRAC notes that there is evidence of an increased risk of suicidality associated with each of the SSRIs, particularly paroxetine and venlafaxine. The committee recommends that SSRI use in paediatric patients with MDD and other psychiatric disorders "be undertaken only within the context of comprehensive management", with monitoring for the development of suicidality. ADRAC also recommends that the Australian product information and recent evaluations of clinical trial data be taken into account when selecting SSRIs for paediatric patients with MDD or other psychiatric disorders, and warn that SSRIs should not be ceased abruptly in paediatric patients being treated for MDD (also see section under ANTIDEPRESSANTS).


TERBINAFINE

Reports of blood dyscrasias

Australia. ADRAC has received a total of 14 reports of blood dyscrasias associated with terbinafine, indicated for onychomycosis, in patients aged 35–84 years (median 65). Of these reports, seven were of agranulocytosis, five of neutropenia and two of pancytopenia, with a time to onset of between 4 and 10 weeks. Recovery was documented in 9 of the 14 reports and, in four cases, occurred within one week of terbinafine discontinuation. The Committee recommends that patients taking terbinafine for longer than one month should be advised to report any symptoms of possible infection, and that if symptoms develop, blood counts should be checked.


TRICYCLIC ANTI-DEPRESSANTS

Overdose risk

Australia. The total quantity of high-dose tricyclic antidepressants that can be obtained by patients at risk of suicide is a concern, reports the ADRAC. Due to concerns regarding the risk of suicide by tricyclic antidepressant overdose, the approved indications in Australia for the 50 and 75 mg preparations of dosulepin (Prothiaden; Dothep), doxepin (Deptran), amitriptyline (Endep) and trimipramine (Surmontil) have been limited to maintenance treatment. These agents remain available for the treatment of major depression, but high-dose tricyclic antidepressants should be limited to patients who are not acutely depressed or suicidal.


Reports in WHO-file: Blood dyscrasias 1
The Twenty-seventh Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring was held from 4 to 6 October 2004, in Dublin, Ireland. As in the previous meetings, participants took part in a working group exercise to answer four pharmacovigilance-related questions:

1. How do focused surveillance methods (for recording adverse drug reactions) assist regulatory decision making? Which focused surveillance method(s) is/are most likely to be helpful in regulatory decision making in your part of the world?

2. In what format should reports from ‘studies’ be sent to the WHO database? What data should be incorporated in such a report and should such data be treated separately? To whom do the data belong?

3. Registries: which registries would be useful in your country? Prioritize these and develop an action plan for creating and implementing the most important ones.

4. Pharmacovigilance Planning – Comments on ICH E2E.

Four groups were formed, with every group discussing all four questions. One facilitator moderated the discussions in each group. Representatives from the four groups later met to pool-together the summary points for each of the four questions. The final observations were put forward as four different presentations, with one speaker addressing each of the four questions. We include here the presentations on the first three questions; the comments on the ICH E2E document were conveyed to the ICH Expert Working Group in Yokohoma, Japan.

**1. How do focused surveillance methods assist regulatory decision making? Which focused surveillance method(s) is/are most likely to be helpful in regulatory decision making in your part of the world?**

The summary of the discussion on the above questions was presented by Dr Henry Fomundam, South Africa.

- Focused surveillance methods (FSMs) are not commonly employed in the developing countries but spontaneous reporting systems exist in most countries. Spontaneous reporting systems have many limitations. However, a well-established spontaneous reporting system could be the starting point for launching a focused surveillance study.
- FSMs have numerous advantages. For example, numerator and denominator information can be obtained, specific type of data (population-specific, gender-specific etc.) could be collected; specific questions could be identified for long-term follow-up; non-serious ADRs can also be captured.
- FSMs are disadvantaged in being, in general, resource intensive, expensive and time consuming.
- The type of FSM that will work best for a particular country will depend on several factors such as specific needs of the country, financial resources, support systems available, knowledge and expertise in the area etc. For example, countries may have special needs to address problems of counterfeiting, populations with special characteristics (e.g. enzyme deficiencies etc.), rare and neglected diseases, mass immunization programmes etc.
- Governments, and in some cases even pharmaceutical companies or private organizations can help fund specific focused surveillance studies.
- It is concluded that FSM and spontaneous reporting systems are complementary but not alternative methods. Together the two systems can strengthen safety monitoring of drugs and the regulatory process.

**Discussion:**

Several issues were raised: It is important to link the results from spontaneous reporting signals and FSM. It is often assumed that FSM is expensive, but the cost involved in FSM is not enormous. Per drug it is more resource intensive, but for the system as a whole it is not. FSMs such as Prescription Event Monitoring can be used not only for raising the questions, but also in soliciting the answers. FSMs not only give you information concerning drug use and ADR, but also provide information about surrogate markers. When it is difficult to measure definite endpoints, surrogate markers could be used instead, in studying those original endpoints. The analysis of the correlation between various markers can be useful for further studies. FSM has different meanings for different countries. It is necessary to define what is meant by focused surveillance methods.
2. In what format should reports from ‘studies’ be sent to the WHO database? What data should be incorporated in such a report and should such data be treated separately? To whom do the data belong?

The results of the discussion for these questions were presented by Mr Mukesh Dheda, South Africa.

- The WHO Collaborating Centre for International Drug Monitoring should develop and make available a user-friendly template for reporting data from focused surveillance studies. It should be flexible and adaptable to a country’s needs and must be field tested.
- Format and data fields should be similar to spontaneous reports. In addition, data fields should indicate the type of surveillance method employed and all other relevant information pertaining to the research question. Personalized data should not be included.
- A registry of all FSM studies carried out by different countries should be maintained and the information should be made available to all member countries.
- The data belong to the country or organization from where they originated. Third parties wishing to use the data should request permission from the originator. Consolidated data from all countries should belong to all National Centres. There should be an agreement on provision and use of data especially if used for commercial purposes.

Discussion:

Changing of field codes has implications for the ICH format. These issues should be discussed at the ICH-E2B meeting. We need to have some transparency concerning the source of the reports. Details on how the data have been collected are important. ADR reports from clinical trials may pose special interpretational challenges (e.g., data from double-blind trials etc.).

3. Registries: which registries would be useful in your country? Prioritize these and develop an action plan for creating and implementing the most important ones

Dr Patrick Purcell, Australia, reported on this discussion.

- A registry is defined as a list of patients sharing the same characteristics. These characteristics could be a disease (disease registry) or a specific exposure (drug registry).
- A registry should involve a systematic collection of defined events in a defined population over a defined period of time. They should include sufficient information to enable a search of patient medical records or linkages with other databases.
- Different types of registries exist and may be used in pharmacoepidemiological studies, in data linkage analyses, in the calculation of incidence rates, to obtain information on disease prevalence, drug usage, off-label usages and outcomes in general.
- Registries on vaccines, prescription drug utilization data, large public health programmes, pregnancy exposure and outcomes and birth defects are, in general very useful.
- Setting up a registry might be resource intensive and expensive to maintain. Countries need to be clear about the objectives and scope of a registry before launching one. The population to be covered, variables to be recorded, expected numerator and denominator data should all be well defined.
- Ownership, access, transparency as well as privacy issues have to be considered.
- The type of registry in a country will largely depend on the ultimate objective of setting up the registry. However, it is not possible to recommend definite ways in which a country could undertake setting up a registry. Complex issues are involved and need to be worked out against the appropriate political and legal framework.

Discussion:

There was a call for making a ‘registry of the registries’, as a first step in bringing together all available registries in different countries.